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A systematic review of sevelamer in ESRD and an analysis of its potential economic impact in Canada and the United States

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Background. The Kidney Disease Outcomes Quality Initiatives (K/DOQI) guidelines on bone metabolism and disease in chronic kidney disease were recently published. Despite limited evidence of clinical effectiveness and without detailed consideration of cost, these guidelines recommend the use of a nonmineral-containing phosphate binder (i.e., sevelamer) in several common clinical situations. The objective of this study is to use the example of sevelamer to outline the information that is needed to assist health care payers with the decision to fund a new and expensive therapy.

Methods. We assessed the clinical benefit of sevelamer by performing a systematic review of all randomized trials evaluating its use. To estimate the direct budget impact associated with implementation of the K/DOQI bone disease guidelines, we used laboratory and medication data available from two cohorts of dialysis patients (one treated in Canada and one in the United States) to determine the proportion of patients who meet the criteria for the use of sevelamer as described in the K/DOQI bone disease guidelines.

Results. No randomized trials document the impact of sevelamer on survival, hospitalization, or quality of life. However, at least 51% and 64% of dialysis patients in the Canadian and American cohorts, respectively, would meet K/DOQI criteria for use of sevelamer. Extrapolating to the United States dialysis population, adoption of the K/DOQI bone guidelines would result in expenditures of approximately $781 million annually on sevelamer alone.

Conclusion. Given their potential budgetary impact, future nephrology clinical practice guidelines should consider resource use, in addition to clinical data.

Key words: economic evaluation, sevelamer, cost-effectiveness, cost, kidney failure, dialysis, hyperphosphatemia.

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Kidney failure has a substantial impact on life expectancy and health-related quality of life (HRQOL) [1, 2]. Although dialysis prolongs life for patients with end-stage renal disease (ESRD), morbidity and mortality remain high in this population. An increasing body of retrospective outcomes research demonstrates an association between hyperphosphatemia, an elevated calcium-phosphate product, hypoparathyroidism [defined as a parathyroid hormone (PTH) level <65 pg/mL] and survival in ESRD patients [3–8]. The purported link to mortality remains inadequately defined but may be mediated through a higher risk of cardiovascular disease [9–12] [abstract; Davies M, et al: *J Am Soc Nephrol* 13:59, 2002].

Attempting to adequately control hyperphosphatemia remains the cornerstone of managing abnormal mineral metabolism in ESRD, including dietary phosphate restriction, the use of oral phosphate binders, and modification of the dialysis prescription. Recent work advocates the use of sevelamer, a nonmineral-containing phosphate binder purported to minimize vascular calcifications [13–16]. It has been suggested that sevelamer may also decrease the incidence and severity of endothelial and soft tissue damage that is associated with the use of excessive oral calcium salts [14, 17].

Structured clinical practice guidelines (CPGs) have been introduced to minimize inappropriate practice variability for the management of mineral metabolism. The Kidney Disease Outcomes Quality Initiatives (K/DOQI) CPGs recommend the use of noncalcium nonaluminium nonmagnesium-containing binders in several common clinical situations [18]. As with many contemporary CPGs, the economics of the intervention, especially in the context of the health care delivery system, were not discussed in the K/DOQI document [18]. This is an especially challenging omission when the CPGs are implemented and monitored through clinical performance measures

(CPMs) [19], which is a mandatory component of CPG implementation [19].

If the cost of all phosphate binders were similar, then the choice of agent might rest only on opinions of comparative efficacy for a patient subgroup. However, sevelamer is several times more expensive than calcium salts, which are the preponderant agents used for hyperphosphatemia in North America. Therefore, information on health outcomes (defined as clinical benefits) and the resources consumed (defined as costs) by this new therapy is critical prior to comprehensive reimbursement [20]. However, since the impact of sevelamer and calcium-based phosphate binders on survival and quality of life is not available, a formal economic evaluation is not feasible. In an effort to summarize available information on the clinical benefit and economic impact of sevelamer, we first performed a systematic review of all relevant randomized trials. Next, using data from dialysis cohorts in Canada and in the United States, we forecast expenditures on sevelamer that would result from adoption of the K/DOQI CPGs on bone metabolism and disease in chronic kidney disease [18].

METHODS

Clinical effects of sevelamer

In assessing the clinical effects of sevelamer, we only considered data from randomized trials, because of the well-known potential for bias associated with observational studies. To identify all trials which randomized ESRD patients to sevelamer versus placebo or active therapy, we searched Medline using the terms "sevelamer" or "Renagel" in databases from January 1969 to May 2003. We also searched the Cochrane Library and the Database of Abstracts and Reviews using "sevelamer" or "Renagel." Last, we examined proceedings from the American Society of Nephrology meetings between 2000 and 2002 and reviewed the reference lists of clinical trials meeting our inclusion criteria for other potentially relevant studies. Any trial that was deemed worthy of manual review was recorded, as well as the reasons for subsequent exclusion (if applicable). The search was not restricted to the English language.

Actual and potential costs of sevelamer and calcium-based phosphate binders

The acquisition costs of sevelamer and calcium-based phosphate binders per patient treated were determined from the *200l Drug Topics RedBook* [21]. We assumed that sevelamer recipients would receive 6.5 g per day, and patients treated with calcium-based phosphate binders would receive 4.3 g per day, which were the mean doses required by subjects in the longest randomized clinical trial [14]. We estimated the potential budget impact of sevelamer based on the recent K/DOQI bone guidelines.

To estimate the budget impact associated with each of the K-DOQI bone disease CPGs, we performed a cross-sectional analysis using prospectively collected data from prevalent Canadian and American patients who required hemodialysis or peritoneal dialysis in June 2002. We determined the proportion of dialysis patients in each population that would meet K/DOQI criteria for the use of sevelamer. Since patient characteristics and clinical practice patterns differ between Canadian and American dialysis populations, we performed these analyses separately for each country.

The Canadian cohort included all hemodialysis and peritoneal dialysis patients who reside within the Calgary Health Region in Calgary, Alberta, Canada (catchment area = 1.0 million persons). In the Calgary Health Region, laboratory, medication and clinical information are captured for all patients with kidney failure using a computerized database [22]. Routine laboratory data are monitored on a monthly basis, and medication data are updated monthly or every 3 months (for hemodialysis and peritoneal dialysis patients, respectively). The use of injectable medications is recorded continuously for all dialysis patients.

The American cohort was comprised of a random sample of patients from Dialysis Clinic Incorporated (DCI), a not-for profit dialysis provider with ~200 dialysis facilities throughout the United States. Laboratory and medication information are collected monthly on average and recorded electronically within a central electronic medical record system. Individual dialysis facilities are directed by the local nephrologist(s) but many procedures, such as the frequency of lab testing are standardized throughout DCI. Serum albumin, calcium, and phosphate are collected monthly while intact PTH is collected on average every 6 months. All laboratory tests are analyzed at a central laboratory. Data on both oral and injectable medications are continuously updated. The population used for this study comprised a random sample drawn from 11,106 dialysis patients who were active in DCI on July 1, 2002.

For these analyses, if more than one laboratory test of interest was measured in a patient during the month of interest, the first test of the month was recorded. The absence of phosphate binders on the medication list was considered to indicate that the patient was not taking a binder at the time of these analyses. Erring on the conservative side, if laboratory data were missing, it was assumed that the patient did not meet the respective criteria for that guideline. Patients who were taking sevelamer were included in the analysis.

One study compared sevelamer recipients in a randomized trial with Medicare beneficiaries (who were not enrolled in a clinical trial and did not receive sevelamer) and found that the former group was less likely to be hospitalized [23]. This benefit was attributed to sevelamer,

Table 1. Design of available randomized trials studying sevelamer

Author	Design	Population	Treatment arm(s)	Control arm	Co-intervention	Follow-up
Chertow et al [27]	Double-blind, randomized, two parallel groups	36 HD on stable dialysis regimens	Sevelamer 1–10 g/day based on previous dose of oral Ca	Placebo	Vitamin D metabolites (unchanged from prestudy dose)	8 weeks
Bleyer et al [28]	Open-label, randomized, cross-over	83 HD on stable doses of Ca or aluminum-based Pi binders	Sevelamer 2.8–5.6 g/day adjusted to serum Pi	2–6 g/day of Ca acetate adjusted to serum Pi	$CaCO_3$ to prevent hypocalcemia	20 weeks
Chertow et al [15]	Open-label, randomized, two parallel groups	71 HD on stable dialysis regimens	Sevelamer 2.8–5.6 g/day and 900 mg/day of elemental Ca adjusted to serum Pi	Sevelamer 2.8–5.6 g/day adjusted to serum Pi	Vitamin D metabolites (unchanged from prestudy dose)	16 weeks
Abstract; Akizawa T et al, *J Am Soc Nephrol* 11:557A, 2000	Open-label, randomized, four parallel groups	94 HD with HPi (6–10 mg/dL)	Sevelamer 1.5 g/day, 3.0 g/day, 6.0 g/day, or 7.5 g/day	—	—	11 weeks
Abstract; Kinugasa E et al, *J Am Soc Nephrol* 12:755A, 2001	Open-label, randomized, two parallel groups	230 HD with HPi (>6.0 mg/dL)	Sevelamer 1.3–7.7 g/day adjusted to serum Pi	$CaCO_3$ 1–5 g/day	—	11 weeks
Chertow, Burke, and Raggi [14]	Open-label, randomized, two parallel groups	200 HD with HPi (>5.5 mg/dL) when all Pi binders were withheld	Sevelamer adjusted to serum Pi and Ca (mean dose 6.5 g/day)	Ca acetate or $CaCO_3$ adjusted to serum Pi and Ca levels (mean doses: 4.6 and 3.9 g/day, respectively)	Dialysate Ca and dose of vitamin D metabolites titrated to serum Ca, Pi, and PTH levels	54 weeks
Sadek et al [29]	Open-label, randomized, two parallel groups	42 HD with PTH <400 pg/mL with $CaCO_3$ as only Pi binder and no vitamin D supplementation	Sevelamer 1.2–4.4 g/day adjusted to serum Pi, dialysate Ca and/or dose of vitamin D adjusted for hypocalcemia	$CaCO_3$ at baseline doses	—	21 weeks

Abbreviations are: HD, hemodialysis; Ca, calcium; $CaCO_3$, calcium carbonate; PTH, parathyroid hormone; Pi, phosphate.

although it is also possible that differences in patient characteristics were responsible. Nonetheless, in the present study, sensitivity analyses were performed to determine the magnitude of reduction in hospitalization that would be required to offset the direct cost of sevelamer [23]. The cost of inpatient care and baseline hospitalization rates for patients with kidney disease were obtained from published literature [24, 25]. It is possible that lower doses of sevelamer might be used in routine clinical practice than in controlled intervention trials, particularly if combination therapy with calcium-based binders is possible in some patients [26]. Therefore, we also considered the budgetary impact of using lower doses of sevelamer.

RESULTS

Clinical effects of sevelamer

We identified 81 trials in the search, of which 21 appeared potentially relevant and were retrieved for review. Five articles fulfilled inclusion criteria (Table 1) [14, 15, 27–29]. We also included two abstracts [abstract; Akizawa T et al, *J Am Soc Nephrol* 11:557A, 2000, and abstract; Kinugasa E et al, *J Am Soc Nephrol* 12:755A, 2001] that fit inclusion criteria, but have not been published as full articles.

Results of the seven randomized trials that were eligible for inclusion are presented in Table 2. Calcium-based binders and sevelamer appeared similarly efficacious as phosphate binders and in controlling the calcium phosphate product [14, 15, 29]. Transient hypercalcemia and suppression of PTH levels were less common with sevelamer, although this was not a consistent finding [14, 28]. Sevelamer delayed the progression of vascular calcification over a 1-year period in a subgroup of hemodialysis patients who had evidence of calcification at baseline [14]. In addition, in one study serum bicarbonate levels were lower in sevelamer recipients, raising concern about the chronic effects of metabolic acidosis [abstract; Akizawa T et al, *J Am Soc Nephrol* 11:557A, 2000].

No studies were identified that examined the impact of sevelamer on mortality or the incidence of cardiovascular events in patients with ESRD [17, 30]. Nor was there direct evidence that sevelamer reduces the incidence of bone related clinical outcomes, such as bone pain or

Table 2. Findings of available randomized trials studying sevelamer

Author	Serum calcium	Serum phosphate	Parathyroid hormone	Calcium-phosphate product	Serum HCO_3	Other clinical effects
Chertow et al [27]	NSD compared with placebo (0 vs. −0.2 mg/dL, P = NS)	↓ compared with placebo (−1.2 vs. +0.2 mg/dL, $P < 0.04$)	—	—	NSD compared with placebo (−0.3 vs. −0.7 mEq/L, P = NS)	↓ in TC and LDL compared with placebo
Bleyer et al [28]	Smaller ↑ compared with Ca acetate (+0.2 vs. +0.6 mg/dL, $P < 0.0001$)	NSD compared with Ca acetate (−2.0 vs. −2.1 mg/dL, P = 0.71)	NSD compared with Ca acetate (−48 vs. −101 pg/mL, P = 0.17)	NSD compared with Ca (−17 vs. −16 mg^2/dL^2, P = 0.66)	—	↓ in hypercalcemia (≥11 mg/dL) compared with Ca acetate (5% vs. 22%, $P < 0.0001$); ↓ in serum TC, TG, and LDL compared with Ca acetate
Chertow et al [15]	NSD compared with sevelamer and $CaCO_3$ group (0 vs. +0.3 mg/dL, P = 0.09)	NSD compared with sevelamer and $CaCO_3$ group (−2.4 vs. −2.3 mg/dL, P = NS)	NSD compared with sevelamer and $CaCO_3$ group (−23 vs. −67 pg/mL, P = 0.07)	NSD compared with sevelamer and CaO_3 group (−22.4 vs. –19.6 mg^2/dL^2, P = NS)	NSD compared with sevelamer and $CaCO_3$ (values not specified)	—
Abstract; Akizawa T et al, *J Am Soc Nephro*l 11:557A, 2000	NSD compared with baseline for any dose regimen of sevelamer	↓ compared with baseline for all four dose regimens of sevelamer	↓ compared with baseline for 3, 6, and 7.5 g/day, but not 1.5 g/day doses (−57, −75, −16, and −23 pg/mL, respectively)	—	—	—
Abstract; Kinugasa E, et al, *J Am Soc Nephrol* 12:755A, 2001	Smaller ↑ compared with $CaC0_3$ (+0.05 vs. +0.59 mg/dL, $P < 0.0001$)	NSD compared with $CaCO_3$(−2.3 vs. −2.3 mg/dL, P = 0.77)	NSD compared with $CaCO_3$ (−57 vs. −124 pg/mL, P = 0.61)	—	—	↓ in hypercalcemia (>11 mg/dL) compared with $CaCO_3$ (0% vs. 16.5%, $P < 0.0001$)
Chertow, Burke, and Raggi [14]	Smaller ↑ compared with oral Ca (+0.1 vs. +0.4 mg/dL, P = 0.002)	NSD compared with oral Ca (−2.5 vs. −2.3 mg/dL, P = 0.33)	NSD compared with oral Ca (−8 vs. −62 pg/mL, P = 0.11)	NSD compared with oral Ca (−23 vs. −20 mg^2/dL^2, P = 0.12)	↓ compared with oral Ca (19.2 vs. 22.1 mEq/L, $P <$ 0.0001)	↓ in TCl and LDL, compared with oral Ca; significantly slower progression of coronary artery and aortic calcification compared with oral Ca
Sadek et al [29]	NSD compared with $CaCO_3$ (−0.05 vs. 0 mg/dL, P = NS)	NSD compared with $CaCO_3$ (+0.03 vs. −0.07 mg/dL, P = NS)	NSD compared with $CaCO_3$ (+53 vs. +54 pg/mL, P = NS)	NSD compared with $CaCO_3$ (+0.05 vs. −0.2 mg^2/dL^2, P = NS)	NSD compared with $CaCO_3$ (−0.7 vs. −0.3 mEq/L P = NS)	↓ LDL cholesterol, compared with $CaCO_3$

Abbreviations are: NSD, no significant difference; NS, nonsignificant ($P > 0.05$); Ca, calcium carbonate; TC, total cholesterol; TG, triglycerides; LDL, low-density-lipoprotein cholesterol.; NR, not reported. Unless otherwise specified, P values refer to effect of sevelamer compared with effect of control group on parameter of interest.

No study reported significant differences in clinical cardiovascular outcomes, health-related quality of life (HRQOL), mortality, or hospitalization rates.

fracture rate. The impact of sevelamer on (HRQOL) has not been tested.

Potential budget impact of sevelamer

Based on an average dose of 6.5 g per day, the average annual cost of sevelamer was $3644 [United States (U.S.)] per patient per year. In comparison, the costs of calcium acetate and of calcium carbonate were $463 U.S. per patient per year and $154 U.S. per patient per year, respectively, assuming an average dose of 4.3 g per day of elemental calcium.

We identified 407 hemodialysis and 92 peritoneal dialysis patients in the Calgary Health Region (Canadian dialysis cohort). The cohort's demographic characteristics were representative of Canadian dialysis patients [31] (data not shown). Laboratory data on serum calcium, albumin, and phosphate was available for 473 (95%) patients while data on intact PTH was available for 388 (78%) patients.

As of September 2002, 60% of patients were using a calcium-based phosphate binder, 1.0% of dialysis patients were using sevelamer, and 28% of dialysis patients were receiving oral or intravenous active vitamin

Table 3. Kidney Disease Outcomes Quality Initiatives (K-DOQI) Guidelines recommending the potential use of sevelamer among patients with end-stage renal disease (ESRD) [18]

Guideline number	Summary of guideline recommendation	Response for analytic model
5	In dialysis patients, if phosphate >5.5 mg/dL despite oral calcium, use a combination of oral calcium and sevelamer	Determine the number of dialysis patients treated with calcium binders with phosphate >5.5 mg/dL
5	In dialysis patients, the total oral calcium dose should be ≤1.5 g/day	Determine the number of dialysis patients whose total $CaCO_3$ dose is >1.5 g/day
5 and 6	In dialysis patients, calcium-based binders should not be used in patients with (a) total serum calcium >10.2 mg/dL or (b) intact parathyroid hormone <150 pg/mL on two consecutive measurements	Determine the number of dialysis patients who are not on active vitamin D, but are on calcium-based binders and who have either (a) total serum calcium >10.2 mg/dL or (b) intact parathyroid hormone <150 pg/mL on two consecutive measurements
6	Keep predialysis serum calcium-phosphate product <55 mg^2/mL^2 by reducing phosphate level	Determine the number of patients whose predialysis serum calcium phosphate product is >55 mg^2/mL^2
13C	If intact parathyroid hormone <100 pg/mL, reduce dose of calcium-based binders (and switch to sevelamer) and vitamin D	Determine the number of dialysis patients who are on calcium binders, but not active vitamin D, and whose parathyroid hormone level is <100 pg/mL

Table 4. The potential impact of Kidney Disease Outcomes Quality Initiatives (K/DOQI) guidelines on use of sevelamer based on a Canadian dialysis cohort

Guideline	Criteria	Number of dialysis patients who meet criteria ($N = 499$)[a]	Number of hemodialysis patients who meet criteria ($N = 407$)	Number of peritoneal dialysis patients who meet criteria ($N = 92$)	Potential cost of sevelamer associated with adherence to each guideline in a hypothetical 500 patient cohort (U.S. dollars)
5	Phosphate >5.5 mg/dL	99 (20%)	87 (21%)	12 (13%)	$361,000
5	Calcium dose >1.5 g/day	81 (16%)	76 (19%)	5 (5%)[b]	$295,000
5 and 6	Calcium >10.2 mg/dL	45 (9%)	38 (9%)	7 (8%)	$164,000
	Parathyroid hormone <150 pg/mL (two occasions over 6 months)	87 (17%)	77 (19%)	10 (11%)	$317,000
6	Calcium-phosphate product >55 mg^2/mL^2	118 (24%)	99 (24%)	19 (21%)	$430,000
13C	Parathyroid hormone <100 pg/mL (one occasion)	75 (15%)	68 (17%)	7 (8%)	$273,000
Any guideline	Patients meeting ≥ one guideline[b]	51%, 95% CI 47–56	54%, 95% CI 49–59	38%, 95% CI 28–49	$933,000, 95% CI 856,000–1,020,000[c]

[a] A small proportion of patients did not have laboratory measurements drawn (5% for calcium/phosphorus, 22% for parathyroid hormone) and were assumed not to meet the criteria for any of the guidelines but were included in the denominator, which provides conservative estimates for sevelamer use.
[b] $P = 0.002$ for binomial test of proportions comparing hemodialysis vs. peritoneal dialysis
[c] Numbers in this column do not sum to $933,000 since patients may meet more than one criteria for use of sevelamer.

D. Thirty-five percent of dialysis patients who were taking calcium-based phosphate binders had serum phosphorus levels >5.5 mg/dL, while 21% of dialysis patients not taking active vitamin D had corrected [32] serum calcium levels >10.2 mg/dL. Table 4 highlights the number of patients in whom K/DOQI guidelines directly or indirectly recommend the use of sevelamer. Based on fulfillment of K/DOQI guidelines 5, 6, or 13C (Table 3), 256 of 499 (51%) patients would meet criteria for use of sevelamer (Table 4).

Assuming an annual cost per patient of $3644 (U.S.), and that all patients meeting criteria for sevelamer received it (i.e., 51% of patients), an additional $933,000 (U.S.) would be spent in this Canadian dialysis cohort. This amount is 5.4% of all health care spending on these 499 patients [24], or $1865 per capita, which is nearly two thirds of the annual amount spent on all nonerythropoietic medications for the entire cohort [$1.42 million (U.S.)] [24]. Extrapolating to the rest of Canada where there are 13,922 dialysis patients [31], adherence to the K/DOQI bone guidelines could result in an expenditure of $26 million on sevelamer.

We next identified a random sample of 1600 hemodialysis patients and 400 peritoneal dialysis patients from DCI (United States dialysis cohort). The demographic characteristics of this cohort were representative of American dialysis patients [33] (data not shown). Laboratory data on serum calcium, albumin, and phosphate was available for 1847 (92%) patients while data on intact PTH was available for 1764 (88%) patients. Table 5 shows the proportion of patients who met the various K/DOQI criteria for the use of sevelamer. Overall, the proportion of patients treated in the United States who met criteria for the use of sevelamer was substantially higher than in Canada (64% versus 51%, $P < 0.001$). Although the majority of guidelines tended to be met more frequently in the United States patients, more substantial differences were noted in the proportion with hyperphosphatemia (30% versus 20%), high calcium-phosphate products (35% versus 24%) and requiring high doses of oral calcium (29%

Table 5. The potential impact of Kidney Disease Outcomes Quality Initiatives (K/DOQI) guidelines on use of sevelamer based on an American dialysis cohort

Guideline	Criteria	Number of dialysis patients who meet criteria ($N = 2000$)[a]	Number of hemodialysis patients who meet criteria ($N = 1600$)	Number of peritoneal dialysis patients who meet criteria ($N = 400$)	Potential cost of sevelamer associated with adherence to each guideline in a hypothetical 500 patient cohort (U.S. dollars)
5	Phosphate >5.5 mg/dL	592 (30%)	491 (31%)	101 (25%)	$539,000
5	Calcium dose >1.5 g/day	586 (29%)	489 (31%)	97 (24%)	$534,000
5 and 6	Calcium >10.2 mg/dL	87 (4%)	59 (4%)	28 (7%)	$79,000
	Parathyroid hormone <150 pg/mL (two occasions over 6 months)	343 (17%)	275 (17%)	68 (17%)	$302,000
6	Calcium-phosphate product >55 mg^2/mL^2	707 (35%)	568 (36%)	139 (35%)	$607,000
13C	Parathyroid hormone <100 pg/mL (one occasion)	316 (16%)	256 (16%)	60 (15%)	$288,000
Any guideline	Patients meeting ≥ one guideline[a]	64%, 95% CI 62–67	66%, 95% CI 63–68	60%, 95% CI 55–64	$1,166,000; 95% CI 1,130,000–1,221,000[b]

[a] A small proportion of patients did not have laboratory measurements drawn (8% for calcium/phosphorus, 12% for parathyroid hormone) and were assumed not to meet the criteria for any of the guidelines but were included in the denominator, which provides conservative estimates for sevelamer use.
[b] Numbers in this column do not sum to $1,166,000 since patients may meet more than one criteria for use of sevelamer.

versus 16%). Of the American patients, 30% were receiving sevelamer. There was no difference in the proportion of patients who met at least one criterion for sevelamer use between patients who were or were not on sevelamer (data not shown).

To comply with the K/DOQI guidelines, sevelamer might be used in 64% of American hemodialysis patients, which would represent an expenditure that is nearly 20% of the capitated fee paid to dialysis providers for regular hemodialysis of patients in the United States. Making the same assumptions used for the Canadian dialysis population, and extrapolating to the entire United States dialysis population of approximately 335,000 patients [33], this would project to $781 million per year spent on sevelamer alone.

To offset the additional cost of sevelamer, hospitalization costs for ESRD patients [24] treated with sevelamer would need to be reduced by 45% for those treated in Canada, and substantially more in the United States. To address the possibility that our projections overestimated the true prevalence of sevelamer use, we repeated analyses using the lower limit of the 95% CI for the proportion of sevelamer-eligible Canadian patients (i.e., 47%). Even in this conservative analysis, $856,000 (U.S.) would be spent on sevelamer locally (4.1% of health care spending for all local ESRD patients). Finally, if the actual dose of sevelamer used was 2.8 g/day [26], rather than the 6.5 g/day used in our baseline analysis, then $402,000 (U.S.) would be spent on sevelamer in the 499 patient Canadian cohort ($803 per capita).

DISCUSSION

Routinely available oral therapies for managing hyperphosphatemia in North American ESRD patients include calcium-containing phosphate binders, aluminum or magnesium-containing binders, and sevelamer, with clear cost differences between the therapies. The K/DOQI guidelines for the management of bone and mineral metabolism recommend sevelamer for use in several common clinical scenarios. Relying on conservative assumptions, and assuming no price discounts are implemented, we project that implementation of the K/DOQI guidelines [18] might result in an annual expenditure of up to $781 million for sevelamer in the United States alone.

Results of our systematic review suggest that sevelamer may reduce transient hypercalcemia, although its impact on hyperphosphatemia, PTH, and calcium-phosphate product, in comparison to the use of calcium-based binders, appeared similar. While a recent meta-analysis conducted by the manufacturers of sevelamer concluded that sevelamer offered superior metabolic control compared with oral calcium [34], this work pooled results from observational and randomized studies, a technique which is prone to bias. Although a decrease in the rate of progression of vascular calcification was observed in a subgroup of sevelamer recipients in a randomized trial [14], the clinical significance of this finding is unknown. No randomized trials document the effect of sevelamer on survival or quality of life. We did not include observational studies in our systematic review because of their well-documented potential for bias.

There are several potential sources of inaccuracy in our projections for expenditures on sevelamer that might occur after the widespread dissemination of K/DOQI guidelines. Our projections are based on a cross-sectional examination of prevalent dialysis patients. It is possible that the proportion of patients meeting criteria for each guideline might vary month to month, thus

Table 6. Minimum information needed to evaluate the cost-effectiveness of sevelamer therapy

Outcome	Parameter
Clinical outcomes	Impact of sevelamer on mortality in patients with ESRD
	Impact of sevelamer on overall health-related quality of life (i.e., possibly due to a reduction in morbidity resulting from bone or cardiovascular disease)
Health care costs	Cost of sevelamer compared with standard phosphate binders
	Other treatment costs[a]
	Cost of induced therapy, such as additional lab tests
	Cost savings due to possible (though unproven) reduction in hospitalization due to less cardiovascular events or fractures
Nonhealth care costs	Cost (or savings) due to improved return to work rates, or a reduction in time costs associated with the need to receive health care

[a] Includes those unrelated to management of bone disease. For example, it has been suggested that sevelamer might reduce costs related to lipid-lowering therapy.

resulting in overestimation of the number of patients who would consistently meet criteria for sevelamer use. Alternatively, it is possible that our projections may underestimate the true costs. For instance, a portion of Guideline 5 states that, "Both calcium based phosphate binders and other non-calcium and non-aluminum containing phosphate-binding agents (such as sevelamer HCl) are effective in lowering serum phosphorus levels (EVIDENCE) and either may be used as the primary therapy (OPINION)." Guideline 5 also states that, "Non-calcium-containing phosphate binders are preferred in dialysis patients with severe vascular and or other soft-tissue calcification (OPINION)." Because these guidelines offer nonquantitative, clinical thresholds for the use of sevelamer, it is possible that the proportion of patients receiving sevelamer in clinical practice will be substantially higher than our estimates.

As is true for any economic model, the financial projections are heavily influenced by the input assumptions. Therefore, sensitivity analyses were performed for several key components. If the optimal dose of sevelamer is reduced by >50% from the amount anticipated from the clinical trials' experiences, by the use of a combination of sevelamer and calcium binders, the costs would still be substantial. Conversely, because patient adherence is typically lower than outside of clinical trials, and physician prescribing practices for medications often are not those recommended in CPGs, it is possible that the doses prescribed may be higher or lower than the 6.5 g/day used for the current models.

The actual cost of an effective medication may not adequately reflect its economic impact if that medication reduces the occurrence of expensive complications [20]. Because sevelamer has been proposed to prevent cardiovascular complications of ESRD, and cardiovascular disease is the principal cause of morbidity and mortality in ESRD patients, the trade-off was examined based on hospitalizations. At least a 45% reduction in hospitalizations would be required to offset the increased costs of sevelamer. We are unaware of any pharmacologic intervention in the ESRD population that has achieved a comparable morbidity effect in a randomized trial.

Clinicians might object to reserving judgment on the benefit of sevelamer until data on hard clinical outcomes are available, on the basis that such delay would needlessly deny potential benefit to patients. However, there are numerous examples of therapies that were supported by theoretical benefits or results of observational data, but yet did not confer benefit to patients when tested in randomized trials. A relevant example for nephrologists is the normalization of hemoglobin using erythropoietic substances, which was strongly supported by clinical intuition and observational data. However, a well-conducted randomized trial ultimately showed that patients who were randomized to the higher hemoglobin concentration had higher rates of vascular access morbidity and nonsignificantly higher mortality [35].

The impact of costs depends on the economic perspective. In Canada, the payer for dialysis-related medications differs by province. In one province, all oral dialysis-related medications are paid for by the Provincial Renal Agency, which negotiates with the provincial Ministry of Health for a fixed sum per patient annually. Addition of a costly medication such as sevelamer, therefore, decreases the ability to pay for other medications, including those of proven benefit for reducing mortality or favorably impacting quality of life. In the United States, there is no single payer for oral medications. Charges for all oral phosphate binders are paid by the beneficiary and/or their employer-based insurance plan, or state-administered Medicaid programs. Under economically constrained payment systems, increasing the costs for one element of care may decrease the ability or desire of the payer to be at risk for others.

There is proposed national legislation to expand Medicare benefits by offering a phosphate binder drug benefit [S1304, Senator John Kerry (D-MA), 2002]. Before embarking on a policy that offers differential reimbursement to sevelamer and would substantially increase program costs, we propose that selected clinical and fiscal outcomes be captured to better define the benefit of sevelamer (Table 6). A randomized, intervention trial is currently being conducted to determine the impact of sevelamer on survival and the incidence

of cardiovascular events in patients with ESRD. Ideally, this study will also prospectively collect economic information.

Few health care delivery systems can fund all desired programs. Choices must be made about which health programs to fund and which ones to forgo. It is the benefits associated with forgone health care programs or opportunities that constitute opportunity costs [20]. Decision-makers might choose to fund sevelamer, but should only do so if it is felt that no other (currently unfunded) intervention would better impact survival or HRQOL of patients with kidney disease. Presently, current data do not permit a judgment as to whether widespread use of sevelamer represents a wise or poor use of resources.

Based on conservative economic models, we propose that implementation of the recommendations on phosphate binders from the new K/DOQI bone metabolism and disease clinical practice guidelines may result in a substantial increment in total annual health expenditures for ESRD in North America. Before widespread adoption of these CPGs occurs, these economic issues should be considered. Moreover, because randomized trials evaluating the impact of sevelamer on conventional clinical outcomes are lacking, decisions to fund this costly new therapy seem premature. The example of sevelamer demonstrates the importance of considering the potential economic cost and feasibility during the creation of future clinical practice guidelines.

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